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Asenapine for schizophrenia and bipolar I disorder

Jana Lincoln, MD, and Sheldon Preskorn, MD

In August 2009, the FDA approved asenapine for treating acute exacerbation of schizophrenia and acute manic or mixed episodes of bipolar disorder with or without psychosis in adults (***Table 1***). Asenapine is the first psychotropic to obtain simultaneous FDA approval for schizophrenia and bipolar disorder. The drug's unique receptor binding profile shows promise in treatment of positive and negative symptoms of schizophrenia with a low risk of extrapyramidal and anticholinergic side effects.

Table 1

Asenapine: Fast facts

Brand name: Saphris
Indications: Acute schizophrenia in adults; acute mixed or manic episodes with or without psychosis associated with bipolar I disorder in adults
Approval date: August 2009
Availability date: Late 2009
Manufacturer: Schering-Plough
Dosing forms: 5-mg and 10-mg sublingual dissolvable tablets
Recommended dose: Schizophrenia: 5 mg twice daily; bipolar disorder: 10 mg twice daily

Receptor binding profile and sublingual delivery distinguish asenapine from other atypical antipsychotics

How it works

Asenapine is an atypical antipsychotic. Although the exact mechanism of these medications' efficacy is unknown, their antipsychotic and antimanic activity is thought to be the result of antagonism of central dopamine receptors. According to dopamine theory proposed in the 1960s:

- dopaminergic hyperactivity in mesolimbic dopaminergic pathways contributes to positive symptoms of schizophrenia—hallucinations, delusions, disorganized thoughts and behaviors, and catatonia
- dopaminergic hypoactivity in mesocortical dopaminergic pathways (prefrontal cortex) contributes to negative symptoms of schizophrenia—alogia, avolition, anhedonia, autism, social withdrawal, attention problems, blunted affect, and abstract thinking difficulty.

Asenapine has high affinity for multiple dopamine, serotonin, noradrenergic α1 and α2, and histamine H1 receptors, where it works as an antagonist. Asenapine's affinity for several serotonin, noradrenergic, and dopaminergic D3 and D4 receptors is higher than its affinity for D2 receptors (***Table 2, page 76***),[1] which distinguishes asenapine from other atypical antipsychotics except clozapine.

Blockade of 5-HT2A and 5-HT2C receptors in prefrontal cortex increases dopamine release in this area; theoretically, this effect should improve negative symptoms. Another mechanism that possibly improves cognition and negative symptoms

Dr. Lincoln is assistant professor and Dr. Preskorn is professor of psychiatry, University of Kansas School of Medicine, Wichita. Dr. Preskorn also is the psychopharmacology Section Editor of CURRENT PSYCHIATRY and president and CEO of Clinical Research Institute, Wichita.

Clinical Point

Asenapine significantly reduced symptoms of bipolar disorder in patients with acute manic or mixed episodes

Table 2

Asenapine's binding affinity for receptor subtypes*

Receptor substype	Affinity [Ki (nM)]
5-HT2A	0.06
5-HT2C	0.03
D1	1.4
D2	1.3
D3	0.42
D4	1.1
α1	1.2
α2	1.2
H1	1.0
M1	8128

*Lower numbers indicate higher affinity
5-HT: serotonin receptors; D1-4: dopamine receptors; α1, α2: noradrenergic receptors; H1: histamine receptor; M1: muscarinic (cholinergic) receptor
Source: Reference 1

is asenapine's antagonism at central α2 noradrenergic receptors. Central α1 noradrenergic receptor antagonism also might be helpful in improving positive symptoms of schizophrenia.[1]

Asenapine's affinity for the muscarinic-1 cholinergic receptors is quite low, and adverse effects associated with antagonism at these receptors—dry mouth, blurred vision, constipation, and urinary retention—are minimal.[2]

Pharmacokinetics

Absorption of asenapine after oral (swallowed) administration is 2%. To increase total bioavailability to 35%, the drug is manufactured as sublingual dissolvable tablets. After sublingual administration, asenapine is readily absorbed and achieves peak plasma concentration in approximately 1 hour. After absorption, 95% of asenapine binds to transport proteins albumin and α1 acid glycoprotein. The half-life of the medication is approximately 24 hours, and steady state usually is achieved in 3 days.

Metabolism creates about 40 metabolites via multiple metabolic pathways; the main ones are glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 (CYP)1A2. Asenapine is a weak inhibitor of CYP2D6, so coadministration of asenapine with other drugs that are substrates or inhibitors of CYP1A2 (eg, fluvoxamine) or CYP2D6 (eg, paroxetine, fluoxetine) should be done cautiously. Because asenapine elimination is biphasic, twice-daily dosing is recommended.[3]

Efficacy in clinical trials

Schizophrenia. Asenapine's efficacy for treating schizophrenia was evaluated in 3 fixed-dose, 6-week, randomized, double-blind, placebo- and active- (haloperidol, olanzapine, and risperidone) controlled clinical trials in adults.[3-5] Subjects in these studies met DSM-IV criteria for schizophrenia and had acute exacerbation of their illness, with Positive and Negative Syndrome Scale (PANSS) total scores ≥60. Symptom improvement was measured after 6 weeks by PANSS total score, PANSS positive subscale, and Clinical Global Impression scale (CGI).

The first trial (n=174) compared asenapine, 5 mg twice daily, to placebo and risperidone, 3 mg twice daily.[3-5] Asenapine was superior to placebo as demonstrated by symptom improvement on all 3 scales. Risperidone showed statistically significant symptom improvement on PANSS positive subscale and CGI but not on PANSS total score.

In the second trial (n=448), 2 fixed doses of asenapine (5 mg twice daily and 10 mg twice daily) and olanzapine, 15 mg/d, were compared with placebo.[3,5] The only statistically significant symptom improvement in the asenapine group compared with placebo was on the PANSS positive subscale among subjects receiving 5 mg twice daily. Improvements measured by CGI and PANSS total score were not statistically significant.

Olanzapine showed statistically significant symptom improvement on all 3 scales compared with placebo. This study is a negative trial for asenapine; asenapine

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Table 3

Percentages of clinical trial patients who experienced adverse effects with asenapine vs placebo

	Schizophrenia				Bipolar disorder (mania/mixed)	
Adverse effect	Placebo (n=378)	Asenapine, 5 mg bid (n=274)	Asenapine, 10 mg bid (n=208)	Asenapine, 5 or 10 mg bid (n=572)	Placebo (n=203)	Asenapine, 5 or 10 mg bid (n=379)
Oral hypoesthesia	1	6	7	5	<1	4
Weight gain	<1	2	2	3	<1	5
Increased appetite	<1	3	0	2	1	4
Anxiety					2	4
Akathisia	3	4	11	6	2	4
Other EPS (excluding akathisia)	7	9	12	10	2	7
Insomnia	13	16	15	15	5	6
Somnolence	7	15	13	13	6	24
Dizziness	4	7	3	5	3	11

EPS: extrapyramidal symptoms
Source: Reference 11

failed to separate from placebo, whereas olanzapine—the active comparator—did.

The third trial (n=448) compared asenapine, 5 mg twice daily and 10 mg twice daily, with placebo and haloperidol, 4 mg twice daily.[3,5] Compared with placebo, asenapine at both doses and haloperidol improved symptoms on all 3 scales. The 10-mg twice-daily dosage did not provide any additional benefits compared with the 5 mg twice-daily dosage.

Bipolar disorder. Asenapine's efficacy for bipolar disorder was established in two 3-week, randomized, double-blind, placebo- and olanzapine-controlled studies in adults with acute manic or mixed episodes with or without psychosis.[3,6-9] Symptoms were assessed using the Young Mania Rating Scale (YMRS) and Clinical Global Impression-Bipolar (CGI-BP) scale.

In both studies, subjects were randomly assigned to receive asenapine, 10 mg twice daily; olanzapine, 5 to 20 mg/d; or placebo. Depending on efficacy and tolerability, the asenapine dose could be adjusted within the dosing range of 5 mg to 10 mg twice daily starting on day 2. Ninety percent of subjects stayed on the 10 mg twice-daily dose. In both studies, asenapine and olanzapine were statistically superior to placebo on YMRS and CGI-BP severity of illness scores.

Currently no evidence supports asenapine's efficacy for maintenance treatment of schizophrenia or bipolar disorder. American Psychiatric Association practice guidelines recommend continuing treatment for a minimum of 6 months after stabilization of acute episodes of schizophrenia or bipolar disorder to prevent recurrence.[10]

Tolerability in clinical trials

Tolerability information provided in this article was obtained from a Clinical Trial Database consisting of 3,350 subjects:[11]

- 1,953 patients participated in multiple dose effectiveness trials (1,480 with schizophrenia and 473 with bipolar disorder manic/mixed episodes)
- 486 subjects were treated for at least 24 weeks

continued

Clinical Point

In 2 of 3 clinical trials, asenapine significantly improved schizophrenia symptoms compared with placebo

Clinical Point

Advise patients to avoid eating or drinking for 10 minutes after taking asenapine

- 293 subjects were treated for at least 52 weeks.

Overall, asenapine was well tolerated (*Table 3, page 83*).[11] The most common adverse effects in schizophrenia trials were akathisia, oral hypoesthesia, and somnolence. The discontinuation rate due to adverse effects in schizophrenia trials was 9% in the asenapine group vs 10% in the placebo group.

Among patients with bipolar disorder, the most common side effects were somnolence, dizziness, extrapyramidal symptoms other than akathisia, and increased weight. The discontinuation rate for subjects treated with asenapine was 10% vs 6% with placebo. The most common adverse reactions associated with discontinuation were anxiety and oral hypoesthesia. Oral hypoesthesia did not occur in the placebo group, and akathisia was the only dose-dependent adverse reaction.

Dizziness and weight gain. Clinically important adverse effects of asenapine include dizziness and weight gain. Dizziness is possibly related to orthostatic hypotension caused by the drug's activity at the α1 receptor (antagonist). To prevent ischemic events or falls with subsequent injuries, use asenapine with caution in hypotensive patients and those with cardiovascular or cerebrovascular problems.

In clinical trials investigating asenapine's efficacy, mean weight gain was greater in patients receiving asenapine than those receiving placebo. In short-term studies, mean weight gain in patients treated with asenapine was 1.1 kg for subjects with schizophrenia and 1.3 kg for subjects with bipolar mania.[3] Mean weight gain in patients treated with placebo was 0.1 kg for subjects with schizophrenia and 0.2 kg for those with bipolar mania.

In a 52-week comparator study of patients with schizophrenia and schizoaffective disorder, mean weight gain was 0.9 kg in the asenapine group vs 4.2 kg in the olanzapine group.[3] In both groups, the greatest weight increase occurred in subjects with body mass index <23.

There were no clinically relevant mean changes in serum fasting glucose, serum fasting triglycerides, fasting cholesterol, transaminases, and prolactin. Thrombocytopenia, anemia, tachycardia, temporary bundle branch block, visual accommodation disorder, oral paresthesia, glossodynia, swollen tongue, hyponatremia, and dysarthria occurred in 1 in 100 to 1 in 1,000 patients.

Contraindications

There are no absolute contraindications to asenapine use; however, the medication is not recommended for treating:

- women who are pregnant if the risks of treatment outweigh the benefits (pregnancy risk C)
- breast-feeding mothers
- patients with severe hepatic impairment (Child-Pugh C).

Asenapine carries the same class warnings and precautions as other antipsychotic medications, including a "black box" warning of increased mortality risk in elderly patients with dementia-related psychosis. Other class warnings include an increased risk of transient ischemic attack and cerebrovascular accidents in elderly patients with dementia-related psychosis; neuroleptic malignant syndrome; tardive dyskinesia; glycemia/diabetes mellitus; hyperprolactinemia; leukopenia; neutropenia; and agranulocytosis.

Because asenapine is associated with QT prolongation, do not administer it with other QT-prolonging agents, such as procainamide, sotalol, quinidine, erythromycin, clarithromycin, methadone, or other antipsychotics.

Dosing

Asenapine is manufactured as 5-mg and 10-mg sublingual tablets. Advise patients to avoid eating or drinking for 10 minutes after taking asenapine.

The recommended starting and target dosage for patients with schizophrenia is 5 mg twice daily. The recommended starting

dosage for patients with an acute mixed or manic episode of bipolar I disorder is 10 mg twice daily; however, this can be reduced to 5 mg twice daily if the patient experiences intolerable side effects.

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Related Resource

- Asenapine (Saphris) prescribing information. www.spfiles.com/pisaphrisv1.pdf.

Drug Brand Names

Asenapine • Saphris
Clarithromycin • Biaxin
Clozapine • Clozaril
Erythromycin • ERY-C, Ery-Tab
Fluoxetine • Prozac
Fluvoxamine • Luvox
Haloperidol • Haldol
Methadone • Dolophine, Methadose
Olanzapine • Zyprexa
Paroxetine • Paxil
Procainamide • Procanbid
Quinidine • Quinidine
Risperidone • Risperdal
Sotalol • Betapace, Sorine

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Clinical Point

Akathisia, oral hypoesthesia, and somnolence were the most common adverse effects in schizophrenia trials

Bottom Line

In clinical trials, asenapine improved schizophrenia symptoms in adult patients experiencing acute exacerbation of their illness. The drug also reduced symptoms in adults with bipolar I disorder, acute manic or mixed episodes with or without psychosis. Asenapine was well-tolerated, with insomnia, somnolence, and extrapyramidal symptoms reported as the most common adverse effects.